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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/753,752	01/02/2001	Jay M. Short	DIVER1200-3	1890

7590 10/16/2003

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/753,752	SHORT, JAY M.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

--Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 9/22/2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____.
3. ☒ Applicant's reply has overcome the following rejection(s): see attached.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-5*.

   Claim(s) withdrawn from consideration: _____.
8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.
10. ☐ Other: _____

ADVISORY ACTION

1. Claims 1-5 are pending.

2. The period for reply continues to run from the date of the final rejection. Any extension of time must be obtained by filing a petition under 37 CRF 1.136(a) accompanied by the appropriate fee. The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. A reply within the meaning of 37 CFR 1.113 must be timely filed to avoid abandonment of this application.

3. The request for entering amendments to claims 1, 3, 5 and arguments filed on 9/22/2003 under 37 CFR 1.116 in reply to the Final Action mailed on 6/18/2003 are acknowledged. The proposed amendments to claims 1, 3, 5 will be entered since they are deemed sufficient to overcome objections and/or 35USC 112, second paragraph rejections previously applied. However, entry of these amendments is not deemed sufficient to place the application in condition for allowance for the following reasons.

4. Claims 1-5 remain rejected under 35 USC 112, first paragraph as failing to comply with the written description requirement. Applicants argue that given the knowledge of the art in regard to enzyme activity tests, one can easily determine whether every clone in the library was given the same positive signal or displaying the same enzymatic characteristic, or whether one or more particular cells were producing a positive response that was not common to the whole library. Applicants submit that a subtraction technique does not at all require use a host cell whose complete genome is unknown but can be accomplish by ignoring or subtracting out the enzymatic activities that are commonly produced by the host cells. According to Applicants one of skill in the art does not need to know the exact temperature or pH at which the host's enzymes cease to function to use the subtraction method since one can increase or lower pH or temperature until enzymatic activity common to all of the host cells has been eliminated and

only the specific expression products that remain at extreme pH and temperature are attributable to the recovered DNA. Applicants also submit that false positives can also be detected in a similar procedure.

5. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. It is noted that the claims as written encompass any host cell and any enzymatic activity. While the Examiner acknowledges that one of skill in the art can raise or lower pH or temperature and eliminate all enzymatic activity in a host cell, it is unclear as to how one can determine which are the temperatures or pH conditions which would eliminate only the host's endogenous enzymatic activity and not that which can be attributed to the "recovered DNA" without some knowledge or guidance as to which enzymes are endogenous to that host cell, such that a temperature/pH range could be established for endogenous enzymatic activity for a particular host cell. If, for example, the host cells and the organisms from which the "recovered DNA" is isolated have a similar temperature/pH range in regard to their endogenous enzymatic activity, it is unclear as to how one can use the subtraction method indicated by Applicants using temperature/pH. In addition, even if one could use the subtraction method as Applicants assert, the specification is silent in regard to how to detect enzymatic activity which is only found at pH and temperatures which are not extremes, nor does it teach how to detect false positive under those conditions. Since the claims encompass any enzymatic activity and any host cell, one cannot reasonably conclude that the claimed invention is adequately described.

6. Claims 1-5 remain rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for identifying E. coli clones of a recombinant DNA library derived from an uncultivated microorganism wherein the clones are screened for hydrolase activity after heating to 70 C, does not reasonably provide enablement for a method of identifying clones of a recombinant DNA library derived from an uncultivated microorganism wherein the clones are tested for expression of any enzyme having any enzymatic characteristic or any protein having any characteristic. Applicants argue that the claims as amended now refer to enzymatic activity/characteristic and not just any protein

characteristic/activity. Furthermore, Applicants submit that the remarks made in regard to the written description rejection also apply to the enablement rejection. Applicants also submit that in regard to claims 4 and 5, detection of enzymatic activity under extreme conditions, such as low/high pH or temperature, is routine. Therefore, Applicants request withdrawal of the enablement rejection.

7. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the enablement rejection. While it is agreed that the claims are now limited to enzymatic activity/characteristics, and that detection of enzymatic activity at low/high temperature/pH is routine if the enzymatic assay is known, the Examiner disagrees with Applicant's contention that the claimed process is enabled. As indicated above, it is unclear as to how one can one can determine which are the temperatures or pH conditions which would eliminate only the host's endogenous enzymatic activity and not that which can be attributed to the "recovered DNA" without some knowledge or guidance as to which enzymes are endogenous to that host cell, such that a temperature/pH range could be established for endogenous enzymatic activity for a particular host cell. See discussion above. The specification is silent in regard to how to detect enzymatic activity which is only found at pH and temperatures which are not extremes, nor does it teach how to detect false positive under those conditions. In view of the fact that the claims encompass any host cell and any the enzymatic activity being detected, one cannot reasonably conclude that the specification is enabling for the full scope of the claimed invention.

8. It is also noted that claims 1-5 would also be rejected under 35 USC 112, first paragraph as containing new matter since the claims have been amended to recite the limitation "two or more uncultivated organisms" in claims 1 and 3, for which the Examiner has not been able to locate adequate support. Thus, there is no indication that the claimed process using DNA derived from two or more uncultivated organisms were within the scope of the invention as conceived by Applicants at the time the application was filed.

9. Claims 1-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yen et al. (US Patent No. 5171684, 1992) in view of More et al. (Appl. Environ. Microbiol. 60(5):1572-1580, 1994). Applicants argue that the claim invention distinguishes from the combined references in that claim 1 requires at least "screening in the liquid phase a library of expression clones randomly produced from DNA of two or more uncultivated organisms". In regard to claim 3, Applicants argue that claim 3 requires: (i) recovering DNA selectively from a DNA population derived from two or more uncultivated organisms by contacting the recovered DNA in a liquid phase assay under hybridizing conditions with at least one hybridizing probe containing a full-length coding region sequence or a partial coding region sequence for an enzyme having the specified enzymatic characteristic, (ii) transforming a host cell with the recovered DNA to produce a library of clones; and (iii) screening for a specified enzymatic characteristic in an expression product prepared by expressing the library of clones to obtain expression products, which are screened to identify the specified enzymatic characteristic. Applicants argue that Yen fails to suggest the invention of claims 1 and 3 because in Yen's method, the isolated DNA was obtained from a single cultured organism and the DNA was pretreated so as to bias the DNA toward a particular known enzyme with a restriction endonuclease whose active site was known to exist in some or all of the genes encoding the predetermined target enzyme. Furthermore, according to Applicants, Yen fails to suggest creating and screening a DNA library that is produced from the DNA of two or more uncultivated organisms or that is randomly produced from DNA of two or more uncultivated microorganisms. In regard to claims 4-5, Applicants submit that Yen does not teach to mutagenize DNA recovered from a mixed population of organisms for formation of a library to be screened for identifying a mutant DNA encoding an enzyme with a specified enzymatic characteristic or having increased pH or temperature stability. Applicants submit that More does not cure the deficiencies of Yen and does not render the claimed invention obvious. According to Applicants, More's disclosure regarding the isolation of DNA from a sediment sample dwells on failure rather than successes. Applicants argue that in view of the

teachings of More, one of skill in the art would not be motivated to develop an assay as disclosed by Yen in which the DNA of a mixed population of uncultivated organisms is substituted randomly for the DNA of a single known and cultivated organism to produce a DNA expression library that is screened to identify clones encoding a desired enzymatic activity. Applicants further submit that in view of the inefficiency and lack of reproducibility taught by More, even if one is motivated to combine the disclosures of Yen and More, one of skill in the art would not have a reasonable expectation of success in identifying clones with DNA encoding an enzyme having a desired enzymatic characteristic.

10. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the obviousness rejection. As clearly indicated in previous Office Actions, the Examiner is relying on the teachings of More et al. in regard to the DNA used in the library. The Examiner is not contending that the DNA of Yen was not obtained from a single cultured organism, but rather that Yen teaches a process for identifying clones of a recombinant P. mendocina KR-1 library where the clones are screened in the liquid phase for toluene monooxygenase activity, i.e. enzymatic activity, using radioactive toluene specificity (column 14, Example 11, Table I) and several other substrates to determine if phenolic compounds were formed, i.e. substrate specificity (column 15-16, Example 12, Table II). More et al. teaches the isolation of DNA from soil microbial populations. Furthermore, More et al. teaches that soil and sediments contain uncultured indigenous microorganisms (page 1572, first column, lines 1-6). Therefore, the limitation "two or more uncultivated organisms" is taught by More et al. In regard to the term "randomly produced", it is noted that the term refers to the clones being produced. As such, this term is implicit since as known in the art, transformation of clones with a DNA library is inherently a random process as (1) not all cells exposed to the DNA will be transformed, and (2) there is no control as to which DNA fragment is going to be present in a particular clone. Therefore, the teachings of Yen and More anticipate the instant claims as written. While it is agreed that Yen does not teach mutagenesis of the DNA prior to transformation of the host cells, as indicated in the Final Action, it would have been

obvious to one of skill in the art to mutagenize the DNA prior to its use in preparing the clones. A person of skill in the art is motivated to mutagenize the DNA before preparing the clones to study the effect of mutations in the function of the corresponding protein and to further characterize the structure-function relationship in the protein. One of skill in the art has a reasonable expectation of success at practicing the method of Yen and More with DNA with is mutagenized prior to its use in the preparation of clones since Yen teaches mutagenesis of PmKR1 cells (column 9, Example 4) and DNA mutagenesis techniques are well known and widely used in the art. Therefore, the claimed invention would have been prima facie obvious. The Examiner disagrees with Applicant's contention that, in view of More's analysis of the limitations in isolating/purifying DNA isolated from soil, one of skill in the art (1) would not be motivated to develop an assay as disclosed by Yen in which the DNA used is that of a mixed population of uncultivated microorganisms, and (2) would not have a reasonable expectation of success in identifying clones with DNA encoding an enzyme with a desired characteristic. While it is agreed that More discloses some limitations in regard to the isolation of DNA from soil samples, More does not teach that one of skill in the art cannot isolate DNA from soil samples. In fact, More et al. teaches the improvement of two key steps in DNA isolation from soil samples (Abstract) and conclude that because PCR amplification was indeed possible, the extraction and purification procedures disclosed were successful (page 1579, first column, lines 22-24). Therefore, one of skill in the art would not only be motivated to combine the teachings of More and Yen, but one of skill in the art would have a reasonable expectation of success in identifying clones with DNA encoding an enzyme with the desired characteristic.

11. The terminal disclaimer filed on 9/22/2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6280926, 6168919, 5958672, 6,528,249, 6,566,050, or any patent granted on Application Number 09/421629, 09/467740, 09/875412, has been reviewed and is accepted. The terminal disclaimer has been recorded. In view of

the submission of the terminal disclaimer, the double patenting rejections previously applied are hereby withdrawn.

12. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: NONE

Claim(s) rejected: 1-5

Claim(s) withdrawn from consideration: NONE

13. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
October 6, 2003

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PRIMARY EXAMINER
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